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Prognostic and predictive factors in recurrent and/or metastatic head and neck squamous cell carcinoma: A review of the literature☆

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ABSTRACT

The pattern of clinical behaviour and response to treatment of recurrent and/or metastatic head and neck squamous cell carcinoma is heterogeneous. Treatment strategies that can be employed vary from potentially curative salvage surgery and re-irradiation to palliative systemic therapies and best supportive care. The advent of new therapeutic options, in terms of more sophisticated surgical approaches and techniques, highly conformal and precise radiation techniques and immunotherapy may offer improved control of disease and longer survival. Moreover, the epidemiological changes during the last decades, including the increase of human papilloma virus-related oropharyngeal primary tumors, are also reflected in the recurrent and metastatic setting. In this complex context the identification of predictive and prognostic factors is urgently needed to tailor treatment, to increase its efficacy, and to avoid unnecessary toxicities. A better knowledge of prognosis may also help the patients and caregivers in decision making on the optimal choice of care. The purpose of our review is to highlight the current evidence and shortcomings in this field.

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1. Background

Recurrent and/or metastatic (R/M) head and neck squamous cell carcinomas (HNSCCs) represent a group of highly heterogeneous patients and tumors. Their therapeutic strategy remains a challenge and may vary widely from salvage surgery or re-irradiation with curative intent, to systemic therapies with a palliative aim, up to the choice not to perform any treatment for the progression of disease (Zafereo et al., 2009; Chang et al., 2017; Janot et al., 2008; Heinonen et al., 2018). Furthermore, the managing multidisciplinary team should consider individual patient preferences, severity of symptoms and comorbidity burden, life expectancy, quality of life, the toxicity of treatment and its consequences in terms of surgical reconstruction or functional limitations. Therefore, the availability of reliable prognostic and predictive factors is of great importance both to guide the therapeutic approach and to inform the patient and the caregivers.

It is important to clarify the difference between the definitions for 'prognostic' and 'predictive', as they are often used interchangeably. A prognostic factor informs about outcome independent of the treatment received, while a predictive marker relates to treatment results according to biomarker positive or negative status (Ballman, 2015). Unlike many other malignant diseases, R/M HNSCCs lack reliable predictive biomarkers.

2. Utility of prognosticators

Treatment of recurrent disease has a poorer survival outcome than at the primary setting. However, favorable long-term survival outcomes are reported in some cases of R/M HNSCCs treated with different modalities (Leeman et al., 2017). Therefore, it is essential to obtain tools for proper selection of patients to treatment programs with different intensity and to offer them the most appropriate treatment modality in order to avoid unnecessary toxicities. For instance, in patients undergoing re-irradiation, comorbidities and pre-existing organ dysfunction, defined as feeding tube or tracheostomy dependency, or soft tissue defect, represent prognostic factors to differentiate between short- and long-term survivors (Tanvetyanon et al., 2009). The median overall survival (OS) rates of patients without any comorbidity or organ dysfunction was 59.6 months compared with 5.5 months among those with both of these 2 risk factors. Similarly, while the median survival time of only 15.6 months has been reported for patients undergoing salvage surgery, a subset of patients (20–40%) will have a long-term survival benefit (Bachar et al., 2010; Hamoir et al., 2017; Tan et al., 2010). Tan et al. found that patients with initial stage IV disease and concurrent local and regional failures had markedly different survival; having both, one or none of these parameters dramatically changed the 2-year survival rate (0%, 49% and 83%, respectively) (Tan et al., 2010). In addition, in patients receiving palliative chemotherapy (CT), favorable predictors for 2-year survival have been described (Argiris et al., 2004a). A small quote of long-term responders (5%) has been reported also in patients receiving first-line palliative CT combined with an anti-epidermal growth factor receptor (EGFR) agent (Vermorken et al., 2014). Immunotherapeutic regimens can elicit durable responses in a subset of patients, but these responses may be also delayed (Chow et al., 2016). Thus, identification of patient-specific features that predict treatment response and durable survival is important from both a clinical and economic perspective.

Meanwhile, the landscape of HNSCCs has changed. On one hand, we are witnessing the epidemiologic shift towards an increased rate of human papilloma virus (HPV)-related oropharyngeal primaries. On the other side, the spectrum of therapeutic armamentarium has widened also in the R/M setting, with the advent of immunotherapy, the evolution of surgical approaches and techniques, the use of modern radiation treatment planning and delivery and the availability of proton- and heavy ion-based radiotherapy (RT). Thus, our review is focused on the evaluation of the existing literature concerning prognostic factors in R/M HNSCC patients. For each therapeutic modality, we also considered, whenever possible, the predictive factors of response.

3. The role of HPV

The prognostic role of HPV in the curative setting remains highly relevant also in the R/M setting. Several groups have reported an improved outcome for relapsed HPV-positive disease treated with CT (Spreafico et al., 2014), CT plus anti-EGFR agents (Vermorken et al., 2013), or with multimodal approaches (Fakhry et al., 2014; Deeken et al., 2015). More specific data will be reported in the following sections.

4. Potentially curative approaches

The strongest prognostic factor in R/M HNSCC is the feasibility of surgical salvage and re-irradiation as the second choice. Interestingly, factors that support the feasibility of these approaches are not clearly defined yet, as the decision often relies on the clinical judgment of the treating physician or the multidisciplinary tumor board, which renders recommendations for treatment. However, some oncologic and clinical issues are recognized as essential in determining if either surgery or re-irradiation are feasible. Some prognostic factors are similar for both types of treatment modalities, while others are specific only for one treatment approach.

Performance status, age and comorbidity status are clinical characteristics that may help physicians in defining the best therapeutic strategy and balancing between expected toxicities and oncologic outcome. As previously reported, comorbidities and organ dysfunction caused by previous treatments and existing disease could well define life expectancy in the R/M HNSCC setting (Tanvetyanon et al., 2009). The Charlson comorbidity index, incorporating also age, showed to be a significant predictor of death within 1 year of salvage treatment (Kim et al., 2015).

Before any choice for salvage treatment with possible curative intent, the presence of distant metastasis should be ruled out with an accurate imaging.

5. Salvage surgery

To achieve a chance on cure by surgery (alone) in recurrent HNSCC, all margins should be clear from tumor. The use of either regional or free-flap reconstruction may offer the opportunity of wider resection and thus achieving more frequently negative margins and therefore, better outcomes. However, wide margins will remain difficult to obtain close to important structures, e.g. carotid artery. Goodwin performed a meta-analysis of 32 studies with a total of 1080 patients (laryngeal 41%, pharyngeal 32%, oral cavity cancer 24%) and reported a 5-year survival rate of 39% (Goodwin, 2000). Similar survival figures have not been reported in the radiotherapy series, which clearly points out the importance of patient selection for salvage surgery and the existence of a selection bias with prognostically less favorable patients being usually directed to non-surgical treatment programs. Patients with unresectable disease (i.e., with extension to prevertebral fascia or skull base or tumor encasing the carotid artery) by definition are not candidates for a curative salvage surgery. However, although it has no role in improving survival, debulking surgery may be considered as a way to palliate symptoms in highly selected cases, for instance in case of airway obstruction.

Several factors have been considered in determining prognosis of R/M HNSCC patients referred for salvage surgery (Table 1).

Recurrent tumor in a previously irradiated or operated field generally has a poor prognosis. The subsite influences the outcome, with laryngeal cancer showing relatively favorable survival outcomes compared with other subsites (Hamoir et al., 2017; Goodwin, 2000; Matoscevic et al., 2014; Ho et al., 2014). Salvage total laryngectomy,

Table 1
Comprehensive list of prognostic factors for salvage surgery identified in literature.

Salvage surgery
T and N stage at recurrence and at initial diagnosis
HPV status
Disease subsite (larynx vs other)
Disease-free interval
Surgical margins
Previous radiation therapy performed
Age
Performance status
Comorbidities

when accompanied by clear surgical margins, can result in 5-year OS rates of 57–70% (Holsinger et al., 2006; Ganly et al., 2006; Sandulache et al., 2016). In contrast, hypopharyngeal cancer has the poorest long-term results after surgical salvage, due to the proximity of critical structures such as the carotid artery or prevertebral fascia that makes it difficult to attain clear surgical margins. Another contributing factor in recurrent hypopharyngeal cancer is the high incidence of distant metastasis. However, the impact of the treated site was found to be less important than the stage of recurrence (Goodwin, 2000). Patients with advanced recurrent primary tumors (rT3–4) and/or advanced recurrent nodal disease (rN2–3) have a poorer outcome as compared with patients with early-stage recurrence (Zafereo et al., 2009; Goodwin, 2000; Ho et al., 2014). This is likely due to the difficulty in obtaining clear surgical margins in cases with higher T classification and by the higher risk of complications due to more extensive surgery. In this regard, the extent and complexity of resections represent indirect negative prognostic factors. In addition, recurrent disease differs from primary tumors as it typically has an infiltrative and multifocal growth, spreading in microscopic deposits extending beyond the initial tumor boundaries, which often preclude the achievement of free margins. Similarly, stage at initial presentation remains prognostic, as higher initial stage of the diseaseis associated with an increased risk of locoregional recurrence and distant metastasis after salvage surgery (Tan et al., 2010; Taguchi et al., 2016). A shorter disease-free interval predicts poorer outcome, as evidenced by several reports (Zafereo et al., 2009; Kim et al., 2015; Liao et al., 2008); generally, an interval of 6 months or less results in poorer patient outcome.

Molecular justifications for these prognostic factors may be identified, applicable also to other treatment settings. As it is well known that R/M HNSCCs have a different molecular profile than primary tumors (Morris et al., 2016), it may be hypothesized that also primary cancers with clinical dismal prognostic factors for survival at recurrence (higher stage, lower disease-free interval) carry more deregulated genomic features than those with better outcomes.

Positive margins or extracapsular spread has an increased risk for recurrence in primary as well as salvage surgery setting; some reports also show close margins as possible negative prognostic factors (Zafereo et al., 2009; Hamoir et al., 2017; Tan et al., 2010; Ho et al., 2014; Nichols et al., 2011). As most recurrences are in previously irradiated areas, this increased risk cannot be always mitigated by adjuvant treatment. Similarly, salvage surgery performed in patients who have already received radiotherapy will result in a worse outcome than when carried out in radiation-naïve subjects. This may be explained by both the limitations in giving adjuvant radiotherapy and the likely increase in radiation-induced cancer mutations resulting in more aggressive behaviour.

Some authors have created a prediction modelling algorithm, which utilizes the aforementioned factors. Hamoir et al. incorporated tumor site, locoregional failure and initial stage in a prediction score that stratified patients into four different disease-free specific survival (DFS) outcomes, which varied between 29% and 96% at 2 years, according to the presence of 3–0 bad prognostic factors (Hamoir et al., 2017). Tan et al. also built a score considering initial stage IV tumors and concurrent local and regional failures: the presence of two factors gave a 2-year OS rate of 0%, while in the absence of any of them the 2-year OS was 83% (Tan et al., 2010). Unfortunately, the model suggested by (Tan et al., 2010) could not be confirmed by Esteller et al. (Esteller et al., 2011) and (Putten et al. (2015)). This may be caused by low numbers and different cohorts of (selected) patients.

Gañán et al. using recursive partitioning analysis-derived have tried to classify patients in function of the possibility of carrying out a salvage surgery (Gañán et al., 2016). Considering initial T classification, location of the tumor (laryngeal vs non-laryngeal), N classification, time to recurrence and initial treatment they stratified patients into four different groups with a possibility of carrying out potentially curative salvage surgery, which varied between 15 and 81% depending on those factors.

The outcome of patients treated with salvage surgery is also influenced by HPV status: in the analysis of Guo et al., HPV-positive cancer patients experienced a more favorable 2- and 3-year OS than their HPV-negative counterparts (79 vs 57% and 67 vs 43%, respectively) (Guo et al., 2015).

In recurrent oropharyngeal cancer, a systematic review and meta-analysis of published trials showed a longer OS in patients treated with potentially salvageable approaches in the post-2000 cohort (Jayaram et al., 2016); this outcome benefit could be primarily due to the increase in HPV-positive cancers over the last two decades and to the improvement in surgical and radiotherapeutic techniques, as well as to better patient's selection. The same Authors also reported a longer 5-year OS in patients receiving surgery as a salvage treatment in comparison to radiation therapy, even if this observation was verified only in cohorts recruited before the year 2000 and again, it could be biased by patient's selection.

In case of recurrence of HPV-positive cancers, it has been proposed that a multimodal intensive treatment, comprising also metastasectomy, could benefit the patients, thus gaining prolonged OS (Deeken et al., 2015). This HPV status should be tested on larger number of patients, to confirm the positive prognostic effect of the multimodal approach in HPV-positive cases.

The treatment approach to patients with oligometastatic disease is often a challenge, as the role of surgical exeresis or radioablation of distant disease is not clearly recognized and most patients are offered systemic treatments. In the future, the identification of prognostic factors for oligometastatic patients and the use of more tailored interventions could prolong OS in these patients. One ongoing phase II trial is comparing stereotactic radiotherapy combined with chemotherapy or not for treatment of oligometastases in HNSCC (ClinicalTrials.gov Identifier: NCT03070366).

6. Re-irradiation

Although salvage surgery is a preferred treatment option in recurrent disease after non-surgical treatment, only a minority of patients are considered candidates for this strategy. However, re-irradiation has attracted more attention as a potential therapy for recurrent HNSCCs with the advent of modern RT techniques, such as intensity-modulated radiotherapy (IMRT) and stereotactic RT. At this point it should be underlined that there are no studies with head-to-head comparisonof outcomes between surgical salvage and re-irradiation in recurrent HNSCCs. Prognostic factors identified in the literature are reported in Table 2. In such a scenario, the cumulative radiation dose and the volume of irradiated tissue must be thought fully considered to limit acute and especially late toxicities. It is not only the dose delivered during previous radiation that is important but also the time elapsed between the two treatments and pre-existing toxicities, i.e. residual late sequelae after the first RT. Because treatment options for alleviation of late sequelae of RT are limited and of variable benefit, the objective

Table 2
Comprehensive list of prognostic factors with reirradiation identified in literature.

Reirradiation
T and N stage
HPV status
Disease subsite (larynx, nasopharynx vs other)
Disease-free interval
Previous RT dose received by critical structure
Treatment late toxicity
Tumor bulk or tumor volume
Salvage surgery feasible
Age
Performance status
Comorbidities

Table 3
Comprehensive list of prognostic factors with chemotherapy identified in literature.

Chemotherapy
Hypercalcemia
Weight loss
Performance status
Response to chemotherapy
Tumor differentiation
Primary tumor site
Previous radiotherapy
Site of recurrence
Time to first recurrence
HPV status

assessment of existing sequelaeand a fair estimate of potential deterioration by additional RT is of paramount importance (Strojan et al., 2017). As recommended in a recent systemic literature review, re-irradiation dose of ≥60 Gy and a volume encompassing the gross tumor with up to a 5-mm margin should be pursued (Strojan et al., 2015). The risk of severe late complications has been reported to be 20–40% and is related to prior RT dose, recurrent tumor site, re-treatment RT dose, treated volume and technique (Yamazaki et al., 2011). The disease subsites with better outcome after re-irradiation are the larynx and nasopharynx (Cacicedo et al., 2014; Takiar et al., 2016). As noted, survival outcome needs to be balanced against the risk of significant treatment-related toxicities that may impact on quality or quantity of life. Choe et al., who analyzed 166 patients re-irradiated for recurrent or second primary HNSCC, identified salvage surgery (before re-irradiation), previous chemo-RT, RT dose ≥60 Gyand the time interval from previous RT of ≥36 months as significant independent prognostic variables for prediction of OS (Choe et al., 2011). The MD Anderson Cancer Center group evaluated the prognostic factors in 206 patients re-irradiated with IMRT and, at multivariate analysis, they found that performance status and response to induction CT are favorable prognosticators of OS, while both nasopharyngeal initial site and response to induction CT positively had positive impact on progression-free survival (PFS) (Takiar et al., 2016). Prognostic scores or nomograms to select patients for re-irradiation have been described by several authors (Leeman et al., 2017; Riaz et al., 2014; Ward et al., 2017). Tanvetyanon et al. reported comorbidities, organ dysfunction, isolated neck recurrence, tumor volume and the interval between completion of previous radiation and initiation of re-irradiation as parameters to predict the probability of death within 24 months after re-irradiation (Tanvetyanon et al., 2009). Using this nomogram, a good agreement between the predicted and the observed outcomes was found with a concordance index (0.75), showing a negligible chance of survival at 2 years after reirradiation for most patients with organ dysfunction and comorbidity and those who did not have an isolated nodal recurrence. More recently, Ward et al. employed the recursive partitioning analysis to discriminate cohorts of patients with distinct survival patterns after reirradiation (Ward et al., 2017). They identified three different classes: those > 2 years after the first treatment with resected tumors regardless of definitive margin status; > 2 years after the first treatment with unresected tumors or within 2 years without organ dysfunction; and those within 2 years but with organ dysfunction; the corresponding 2-year OS were 62%, 40% and 17%, respectively. Lastly, Riaz et al. built a nomogram to predict locoregional control after re-irradiation: they suggested to employ this tool for discrimination between the choice of re-irradiation with curative or palliative intent (Riaz et al., 2014). The factors involved were stage of recurrent disease, site of recurrence (oral cavity carrying a worse prognosis), presence of organ dysfunction, salvage surgery and RT dose. HPV status confirmed its positive prognostic role also in patients re-irradiated for recurrence (Davis et al., 2014; Velez et al., 2018).

Several authors reported that previous treatment with concurrent chemo-RT was predictive for worse OS after re-irradiation (Choe et al., 2011; Nagar et al., 2004), possibly due to more pronounced proliferation of fibrous tissue in the treated area after intensive chemoradiation and/or the presence of a highly RT-resistant tumor clones in recurrent tumor that survived initial chemo-RT. In poorly vascularized fibrotic regions, drug delivery is compromized and RT-resistant hypoxic areas are more extensive, which both reduce effectiveness of subsequent treatment.

7. Systemic therapies

7.1. Chemotherapy

Table 3 resumes the main prognostic factors associated with survival in patients treated with CT for R/M HNSCCs. The prognostic role of cancer-related hypercalcemia (CRH) in advanced solid tumors has been analyzed in depth, particularly in R/M HNSCCs (Degardin et al., 1995; Penel et al., 2008, 2009; Le Tinier et al., 2011; Liaw et al., 1990; Ramos et al., 2017). Globally, CRH was linked to dismal OS ranging from 35 to 91 days. Ramos et al. also demonstrated that systemic CT, given after diagnosis of CRH, when feasible, leads to a meaningful improvement in OS (144 days in CT-treated patients vs 25 days in no-treated cohort; p = 0.001) (Ramos et al., 2017); however, existence of selection bias in this report is rather possible. The gain of OS from response to CT in R/M HNSCCs was described more than 25 years ago (Ramos et al., 2017). Moreover, the two factors determining OS were performance status and weight loss. These results were consistent with what was observed by Argiris et al. in the largest retrospective analysis of prognostic factors in R/M HNSCC patients treated with CT (Argiris et al., 2004a). In multivariate analysis, additional three predictors of poorer OS were identified: hypopharynx and oral cavity subsites, well-to-moderate tumor differentiation and prior RT. After having added response to CT into this prognostic model, all factors maintained their statistical significance except for primary tumor subsite. Furthermore, in overall response rate analysis, residual disease at the primary site after first treatment with curative intent negatively impacted on outcome.

When patients were divided between those with 0–2 negative prognostic factors and those with 3–5, the OS was markedly different (median OS: 0.98 vs 0.52 years, respectively). Among 399 patients included in the Argiris' analysis, only 13% were elderly (≥70 years old) but age influenced only toxicities and not the survival outcomes (Argiris et al., 2004b). Stell and McCormick identified two other important predictors of OS, which were not previously described: site of recurrence (recurrence with distant metastasis had worse outcome than relapse at the primary tumor site and the neck area) and time elapsed from primary treatment to recurrence (Stell and McCormick, 1986).

From a biological point of view, the expression of EGFR ligands showed a prognostic impact in patients treated with CT: a higher detection rate (by immunohistochemistry) of amphiregulin was linked to

worse prognosis with lower disease control rate and significantly shorter PFS and OS (Tinhofer et al., 2011). These data, despite being very intriguing, still need to be validated as they come from a retrospective analysis.

Spreafico et al. pooled the data of patients enrolled in three clinical trials, analysing only CT-treated patients, to study the impact of HPV status on the survival outcomes of R/M HNSCCs (Spreafico et al., 2014). Even if the rate of HPV-positive patients was low (7–16% of the enrolled patients in these trials), they found that HPV conferred a favorable prognosis in CT-treated R/M HNSCCs (hazard ratio [HR] for p16+ = 0.70; 95% CI: 0.52–0.93).

7.2. Anti-EGFR agents

In studies with anti-EGFR therapies for R/M HNSCCs, a prognostic role of EGFR has never been identified, despite analysis of *EGFR* activation, expression, gene copy number and mutation (Bossi et al., 2016a). To date, only rare *EGFR* polymorphisms confer a survival advantage, mainly dictated by the specific polymorphism *EGFR* R521 K. In a phase II trial of R/M HNSCC patients treated with docetaxel plus cetuximab, as second-line treatment, this *EGFR* polymorphism was able to predict higher skin toxicity and an increased disease control rate with longer PFS, however, without benefit in terms of OS (Klinghammer et al., 2010). An OS advantage was reported in a second study in patients with advanced HNSCCs, carrying the same polymorphism and treated with cetuximab ± CT (Stoehlmacher-Williams et al., 2012).

The whole transcriptome-based approach identified patients who obtained a long-term response to EGFR inhibitors in combination with CT (Bossi et al., 2016b). Tumor samples of patients experiencing long PFS were enriched in expression of genes involved in *EGFR* signalling, in intracellular catabolic processes, in tissue development including upregulation of the epidermal differentiation complex genes; in contrast, the main gene-expression profile of short-term responders to treatment was characterized by high expression of *KRAS* signalling genes. This potentially predictive model of cetuximab sensitivity has also been integrated and confirmed by miRNA analysis (De Cecco et al., 2017).

In this scenario of prediction of response to anti-EGFR therapies, the same group also detected specific transcript fusions in cetuximab-sensitive patients (i.e. long noncoding RNA-containing fusions enriched only in this subgroup) and in those refractory (i.e., CD274–PDCD1LG2 expressed in half of cetuximab-resistant patients without enrichment in the cetuximab-sensitive group) (Bossi et al., 2017).

The prognostic role of HPV status is retained also in R/M HNSCC patients when treated with anti-EGFR agents (Spreafico et al., 2014; Bonner et al., 2017). However, when cetuximab is employed as single agent and not synergizing with CT or radiation, the therapeutic benefit seems to be confined to HPV-negative cases (Szturz et al., 2017).

7.3. Immunotherapy

In the last few years, several new investigational drugs have been studied for HNSCC (Bossi and Alfieri, 2016), but the therapeutic armamentarium of this cancer has been mainly enriched by the immunotherapeutic agents (i.e. anti PD-1/PD-L1 agents). Unfortunately, the benefit of immunotherapy is limited with approximately one out of 5 treated patients who respond to these novel compounds. Adding the fact that at the current cost, these drugs are not cost effective (Tringale et al., 2017), it is of paramount importance to identify the characteristics of the patients and their disease responding to this treatment.

7.3.1. PD-L1/PD-L2 expression

In HNSCCs, regardless of any treatment performed, the significance of PD-L1 expression is yet to be defined. A recent meta-analysis (Li et al., 2017) of 17 cohort studies (total number of patients = 2869) did not find any survival (OS and DFS) difference between PD-L1-positive and -negative HNSCC patients. By subgroup analyses, the authors identified a poorer survival outcome only for PD-L1 positive patients from Asia (worse OS and DFS) and in those with tumors arising from oral cavity (OS) or larynx, nasopharynx and salivary glands (DFS). On the contrary, a negative prognostic role of PD-L1 overexpression on circulating tumor cells has been identified at the end of treatment with curative intent (induction chemotherapy followed by concomitant chemoradiation) in locally advanced HNSCCs (Strati et al., 2017).

Given these observations, when patients with R/M HNSCC are treated with immunotherapy, PD-L1 expression appeared to be a predictive factor for response. Notably, a higher PD-L1 expression is related to longer survival, both with nivolumab and pembrolizumab treatment. In CheckMate-141 (Ferris et al., 2016), the phase III trial of nivolumab in platinum-refractory R/M HNSCCs, where PD-L1 was detected only on tumor cells, OS of patients whose tumors expressed PD-L1 > 1% was 8.7 months (HR: 0.55; range: 0.36–0.83), while it was 5.7 months in those with PD-L1 ≤ 1% tumors (HR: 0.89; range: 0.54–1.45).The clinical benefit of PD-L1 positivity was also confirmed in 2-year survival update of the CheckMate-141 (Ferris et al., 2018): 45% of risk of death less in tumors expressing PD-L1 > 1% (HR [95% CI] = 0.55 [0.39-0.78]) in respect to 27% reported in PD-L1 ≤ 1% tumors (HR [95% CI] = 0.73 [0.49–1.09]). However, it should be underlined that CheckMate-141 trial was not statistically powered to properly detect an OS difference between PD-L1 positive and PD-L1 negative patients. In the same nivolumab-treated population, Harrington at al (Harrington et al., 2017) also demonstrated a better preservation of the patient-reported outcomes (PRO) when compared to patients undergoing CT. The stabilization of symptoms and ability to obtain a functioning status are of primary importance when evaluating salvage therapy and may offer a prognostic tool to decide whether or not to treat this fragile and heavily pre-treated patient population.

In Keynote-040 trial, the phase III trial of pembrolizumab in platinum-refractory R/M HNSCCs, patients carrying a disease with PD-L1 tumor proportion score (TPS) ≥50% had a median OS of 11.6 months with pembrolizumab and 7.9 months with standard of care therapy (HR: 0.54; range: 0.35–0.82) (Cohen et al., 2017). The method for detection of PD-L1 also seems to play a role. In KEYNOTE-012, a phase Ib study with pembrolizumab, PD-L1 was measured on tumor cells only as well as on both tumor and immune cells (e.g. mononuclear inflammatory cells: stromal, T-lymphocytes, etc), the latter expressed as Combined Proportion Score (CPS). Overall response rate (ORR) and efficacy (OS + PFS) were higher in CPS PD-L1 ≥ 1% compared with measuring PD-L1 on tumor cells only (TPS ≥ 1%) (Chow et al., 2016). Therefore, the immune cells involved in antitumor vigilance should be considered since they possibly impact on response to anti-PD-1/anti PD-L1 agents and their respective survival outcomes. In fact, in Keynote-048 (Burtness et al., 2018), a phase III trial with 3 arms of mono-immunotherapy (pembrolizumab), immunotherapy combined with chemo (pembrolizumab plus carboplatin or cisplatin + 5-fluorouracil) and standard of care for first-line of R/M HNSCC (extreme regimen), both CPS ≥ 20% and CPS ≥ 1% resulted predictors of higher OS in patients treated with pembrolizumab when compared to the standard Extreme schedule: (for CPS ≥ 20%, HR [95% CI] = 0.61 [0.45-0.83] while for CPS ≥ 1%, HR [95% CI] = 0.78 [0.64-0.96]).

Two additional, anti-PD-L1 agents have been described that demonstrate safety and efficacy in R/M HNSCCs: atezolizumab (Balheda et al., 2017) and durvalumab [732]. In a phase Ia study with atezolizumab (Balheda et al., 2017), PD-L1 > 5% patients (n = 25) had better ORR (24%) and duration of response (DOR; 26.2 months) than PD-L1 < 5% patients (n = 7; ORR: 14% and DOR: 7.4 months). A phase II study with durvalumab (Zandberg et al., 2017) has been designed selecting only patients whose tumors are highly PD-L1 positive (> 25%, measured on tumor cells only) and reported 13.5% of ORR (15 out of 111 evaluable patients).

Another emerging prognostic factor, which is currently under investigation, is PD-L2. This target was detected on the cell surface of

seven tumor types (Yearley et al., 2017): gastric, melanoma, kidney, bladder, lung, breast (triple-negative) and HNSCCs. The latter was the most PD-L2 enriched tumor type. PD-L2 expression could be a strong predictive factor regardless of PD-L1, thus partially explaining responses in PD-L1-negative patients. In fact, patients with PD-L2-positive tumors cells had longer PFS and improved OS compared with patients with PD-L2-negative cells. Further prospective studies are awaited in this setting.

7.3.2. Hpv

With regards to the impact of HPV status, the nivolumab study (Strati et al., 2017) stated that patients with HPV + tumors resulted more likely to benefit from immunotherapy (HR for death [0.56] in HPV + compared with HR [0.73] in HPV-) but this was not confirmed in the 2-years long-term survival update (Ferris et al., 2018).

Other studies have reported data in this regard. Specifically, in other immunotherapy clinical trials with recurrent HNSCC patients (Chow et al., 2016; Bauml et al., 2017), a trend towards a higher ORR in the HPV + subgroup was observed while it was not confirmed in the atezolizumab (Balheda et al., 2017) and KEYNOTE-040 studies (Cohen et al., 2017). For the time being, HPV status should not be used in selecting R/M HNSCC patients to be treated with immunotherapy.

7.3.3. Microbiome

In the nivolumab trial (Ferris et al., 2016), no difference was shown in the composition of saliva microbiome between responders and non-responders patients.

Having said that, we need to highlight how salivary microbiome profiling of the CheckMate-141 trial was just exploratory.

Considering also that the sample size was small, no final conclusions can be drawn. Therefore, further evidence is urgently needed, as there are no data available with regards to gut microbiome.

7.3.4. Immuno-signature

Other immuno-signatures may also predict treatment response. For example, HNSCC tumors that express the IFN-gamma 6-gene expression signature (*IDO1*, *CXCL9*, *CXCL10*, *HLA-DRA*, *STAT1* and *IFNG*) showed a higher response rate to immunotherapy and a longer PFS and OS when compared to those without this gene signature (Seiwert et al., 2015). Ayers et al. recently identified an IFN-gamma 18-gene signature predicting outcomes in HNSCC patients treated by drugs acting on the PD-1/PD-L1 axis (Ayers et al., 2017). IFN-gamma is reported to increase PD-L1 expression, thus leading to the possibility to better exploit drugs with activity on the PD-1/PD-L1 axis.

7.3.5. Tumor mutational burden

Tumor mutational burden (TMB) is another upcoming biomarker potentially predicting outcomes in immune-oncology which deserves consideration in this context. In general, we have learned that higher TMB is correlated to higher probability of response to PD-1/PD-L1 axis inhibition (Yarchoan et al., 2017). This is explained by the fact that highly mutated tumors may have higher neoepitopes exposure thus possibly increasing the immune response amplified through PD-1/PD-L1 inhibition. This relationship between TMB and response to PD-1/PD-L1 inhibition was also confirmed in virus negative cohort [HPV and Epstein–Barr Virus (EBV)] of HNSCC (Hanna et al., 2018; Haddad et al., 2017). Specifically, in the virus-related group of HNSCC, viral neoepitopes seem to be dominant versus somatic neoepitopes in the process of immune system evasion (Haddad et al., 2017). Furthermore, Hanna et al (Hanna et al., 2018) identified specific somatic frameshift events (insertion and/or deletion of a nucleotide in a translating coding triplet) in tumor suppressor genes able to significantly predict response to PD-1/PD-L1 blockade. Haddad et al (Haddad et al., 2017) did not found a correlation between TMB and tumor inflammation biomarkers [IFN-gamma gene-expression profile (GEP)] in predicting immune response in the HNSCC group. This is different from other cancer types (Long et al., 2018), possibly due to the highest median intratumor infiltration of immunosuppressive Treg/CD8 + T cells, as reported for HNSCC (Mandal et al., 2016).

8. Conclusions

In HNSCCs, the latest epidemiological changes and the introduction of new therapeutic modalities are leading to different prognostic and therapeutic scenarios for R/M disease. The ability to better define the prognosis and likelihood of response for an individual patient should allow more tailored therapeutic approaches, therebyavoiding treatment modalities unlikely to be successful. This would consequently spare patients from unnecessary risks of toxicities and the national healthcare systems from avoidable costs. Furthermore, the identification of more specific prognostic or predictive markers is also important from the clinical research perspective. In this area, these factors could be used as stratification variables within the clinical trials to optimize the study design and better understand the results. Moreover, the combination of multiple factors may also deserve investigation as a novel strategy to potentiate the ability in predicting patients' response or prognosis. However, the routine use of predictive and prognostic biomarkers in clinical decision making demands high levels of evidence to ensure their validity. In that case, reliable prognostic or predictive information might also be very helpful in discussions with patients and their families when deciding on the best possible treatment scenario in the setting of R/M HNSCC.

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